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# Idiotype Vaccination Following ABMT Can Stimulate Specific Anti-Idiotype Immune Responses in Patients With B-Cell Lymphoma

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## ABSTRACT

**Vaccination with the idiotype (Id) protein derived from B-cell malignancies can produce Id-specific immune responses that correlate with improved remission duration and survival rates in patients with follicular non-Hodgkin's lymphoma (NHL). A state of minimal or no residual disease correlates strongly with the laboratory detection of a cellular or humoral immune response. High-dose cytotoxic therapy (HDCT) with autologous stem cell support (autologous bone marrow transplantation [ABMT]) can provide profound cytoreduction of B-cell NHL, but the potential immune suppression associated with myeloablative therapy may compromise a patient's ability to mount a specific immune response. To determine whether patients with NHL could mount detectable immune responses following ABMT, Id vaccines were administered at 2 to 12 months following myeloablative therapy to a series of patients with relapsed or resistant B-cell NHL. Two different vaccination strategies produced robust immune responses against KLH in all patients, supporting the capacity of the reconstituted immune system following HDCT to react against a strong antigen. Combining the results from both vaccination strategies, 10 of 12 patients mounted Id-specific humoral or cellular responses. Vaccinations were consistently well tolerated. Of the 12 patients, 7 have experienced prolonged remissions with a follow-up from HDCT ranging from 3 to more than 11 years. Our experience serves to document the ability of the recovering immune system to react against both self and xenotypic antigens and supports the feasibility and safety of antigen-specific vaccination following myeloablative therapy in patients with B-cell NHL.**

## KEY WORDS

KLH • Idiotype vaccination • Anti-Id response • Non-Hodgkin's lymphoma

## INTRODUCTION

The immunoglobulin (Ig) molecule on the surface of a clonal B-cell non-Hodgkin's lymphoma (NHL) can be used as a tumor-specific target for immunotherapy [1]. Each tumor expresses a unique Ig receptor that contains a specific antigen-recognition region (the idiotype [Id]). This Id protein can be recognized as a strong antigen by a different species, but is a weak antigen in autologous systems [1-4]. Murine models have shown that vaccination with a tumor-specific idiotype can prevent the growth of inoculated tumors [2,4,5]. In clinical evaluations, patients treated with Id vaccines who mount specific anti-Id immune responses have experienced significantly prolonged remissions and survival compared to patients who do not mount such responses [6] or compared to historical control subjects. Furthermore, there has been evidence of a molecular response following Id vaccination, in which polymerase chain reaction (PCR)-detectable tumor markers present before vaccination can no longer be found after such therapy [7,8]. Randomized controlled trials designed to define the efficacy of Id vaccination are in progress.

A strong inverse correlation exists between the presence of a radiographically detectable tumor at the time of vaccination and the laboratory detection of a cellular or humoral Id-specific immune response [6]. The apparent increase in immune responsiveness of patients in complete remission at the time of vaccination suggests that a vaccine approach would be most effective in patients with minimal or no detectable residual

disease. The administration of high-dose chemotherapy with stem cell rescue to achieve maximal cytoreduction is a logical extension of this approach, potentially allowing for an improvement in the efficacy of Id vaccination.

However, there are theoretical concerns that immune reconstitution may be incomplete in the months following such therapy, potentially limiting a patient's ability to mount a significant and antigen-specific immune response. Current data addressing this issue are limited. There are decreases in Ig levels for a period of months to years [9] and a prolonged alteration in the normal T-cell profile [10,11] following high-dose cytotoxic therapy (HDCT). Results from vaccinations for infectious disease in the allotransplantation setting suggest that the recovering immune system is able to mount immune responses against infectious agents after 3 months of recovery [12]. Vaccinations with an inactivated varicella vaccine given only 1 month post–marrow infusion can induce cellular immunity, and 3 monthly administrations of vaccines have been able to reduce the severity of viral reactivation [13]. In the autologous transplantation setting, cytolytic T-cell responses against Epstein-Barr virus (EBV)-transfected cell lines also recover within 3 months [14]. Humoral responses against strong xenoantigens, such as murine proteins and plant toxins, develop with intravenous exposure 4 months post–marrow infusion [15]. In a murine syngeneic marrow transplantation model, immunity against the idiotype can be generated in the donor and transferred to the recipient with consequent protection from tumor challenge [16,17]. However, there is a paucity of similar data on vaccination against tumor antigens after myeloablative therapy with autologous stem cell support in humans.

To explore the practical feasibility of giving Id vaccinations to patients with NHL following HDCT and to determine whether such vaccinations could indeed induce measurable immune responses in this setting, 2 different vaccination regimens were employed. An initial patient cohort received subcutaneous protein vaccinations of Id-KLH in adjuvant (a formulation of Syntex aduvant formulation or SAF) [18], a regimen we have used extensively that has been effective in stimulating immune responses outside the myeloablative setting [6,19]. When a practical technique to administer antigen-primed dendritic-cell vaccinations was first developed [20-22], it proved to be a potent way to stimulate specific cellular immune responses that could induce regression of lymphomas [7]. In a subsequent cohort, a regimen was incorporated that combined both Id-pulsed dendritic cells and subcutaneous protein vaccination following myeloablative therapy. The results suggest that patients are able to mount strong and specific immune responses in response to either vaccination regimen after HDCT, establishing the feasibility of this approach.

## MATERIALS AND METHODS

### Patients

All patients had relapsed or refractory B-cell lymphoma and all patients had developed rapid disease progression or transformation, which supported the use of HDCT with stem cell rescue. The myeloablative regimens varied by institutional standard. They included both chemotherapy and total body irradiation. Vaccination was initiated 2 to 12 months after transplantation, dependent on marrow recovery (recovery of total white blood cell count to greater than 3000 cells/mL and independence from transfusion) and vaccine availability and followed 1 of the 2 administration schedules described below. Patients have subsequently been monitored both clinically and radiographically for relapse.

### Vaccine Formulation

The Id protein was produced by fusion of fresh tumor cells to a heterohybridoma (K6H6-B5) with subsequent selection for the tumor-derived Ig protein (Id) as previously described [23]. Id protein was conjugated to KLH with glutaraldehyde and administered in SAF adjuvant as previously described [6,19]. Id-pulsed autologous dendritic-cell infusions consisted of autologous mononuclear cells collected by leukapheresis and enriched for dendritic cells by gradient centrifugation in the absence of cytokines, as previously described [7,22]. These cells were pulsed with whole Id protein over 36 to 40 hours and then reinfused into the patient [7,24,25]. A total of 1 million to 10 million dendritic cells (defined by high expression of HLA-DR molecules but lacking the lineage-specific markers for monocytes) were reinfused with each vaccination.

### Vaccine Treatments

Vaccination was initiated 2 to 12 months following stem cell reinfusion. Eight patients received Id-adjuvant vaccination alone. These patients received 5 subcutaneous vaccinations, 4 given monthly with the fifth administered as a boost 2 months after the fourth vaccination. Four separate patients received a combination of dendritic-cell and Id-adjuvant vaccinations by the following schedule: 2 protein-pulsed dendritic-cell infusions followed by 5 Id-adjuvant vaccinations, all given at monthly intervals.

### Humoral Responses

Serum anti-Id antibodies were measured by enzyme-linked immunosorbent assay (ELISA) as previously described [6]. Briefly, tumor Id protein and isotype-matched controls were coated onto microtiter plates. $F(ab')_2$ fragments were used when the tumor Id protein was of the IgG isotype. Pre- and postimmunization sera were serially diluted and allowed to bind to the plates. Antibody binding was detected by mouse anti-human IgG horseradish peroxidase (HRP) (TAGO, Burlingame, CA). Anti-KLH antibodies were detected by a sandwich ELISA, using KLH as the target and HRP-labeled KLH as the detection molecule. A 4-fold increase in anti-Id antibody titer compared to the prevaccination serum level and binding to irrelevant isotype-matched proteins was defined as positive. A titer greater than 0.5 μg/mL (determined by comparison of sample results to a standard curve of known concentrations of anti-KLH antibody) was considered positive for induced anti-KLH antibodies.

### Cellular Proliferation Assay

Proliferation of peripheral blood mononuclear cells in response to Id protein was measured using $[^3H]$-thymidine incorporation as previously described [6,25]. Cells were incubated with media alone as the control, or with whole protein (either tumor-derived Id or isotype-matched Ig as a specificity control) with the addition of fresh media containing

**Table 1.** *Characteristics of Study Patients**

| Patient No. | Histology† | No. of Prior Therapies‡ | Resistant to Last Chemotherapy?§ | Time From BMT to Vacc, mo |
|---|---|---|---|---|
| 1 | FSC/DLC | 2 | No | 12 |
| 2 | FSC/FLC | 4 | Yes | 3 |
| 3 | FSC/DLC | 3 | Yes | 11 |
| 4 | DLC | 3 | No | 2 |
| 5 | DLC | 5 | No | 2 |
| 6 | DLC | 2 | No | 5 |
| 7 | FM/IMM | 2 | Yes | 6 |
| 8 | FLC | 3 | No | 11 |
| 9 | FM/DLC | 3 | Yes | 6 |
| 10 | FM | 2 | Yes | 6 |
| 11 | FSC | 4 | Yes | 6 |
| 12 | FM | 3 | Yes | 6 |

*BMT indicates bone marrow transplantation; Vacc, vaccination; FSC, follicular small cleaved; DLC, diffuse large cell; FLC, follicular large cell; FM, follicular mixed cellularity; IMM, immunoblastic.

†Dual histologies denote transformation to more aggressive classification.

‡Including the cytoreductive regimen used immediately prior to myeloablative therapy.

§Developed tumor progression during previous therapy.

interleukin (IL)-2 (Cetus Corporation, Berkeley, CA) so that the final concentration of IL-2 was 30 IU/mL on day 3. [$^3$H]-thymidine was added to the culture on day 5, and cells were harvested on day 6. Incorporation of more than 2 times the background on 2 or more occasions was required for interpretation as positive.

## RESULTS

### Patient Characteristics

Disease and treatment features of all 12 subjects are listed in Table 1. All patients started the series of injections within 1 year of HDCT. All patients had progressive disease prior to their autologous bone marrow transplantation (ABMT) and most had developed resistant lymphomas defined by disease progression during chemotherapy. Fractionated total body irradiation (FTBI) was included as part of the HDCT in 11 of 12 patients (all except Patient 4). High doses of cyclophosphamide, ifosfamide, etoposide, or BCNU were also given as part of the transplantation procedures. All patients were in complete remission following HDCT and prior to vaccination.

Of the 8 patients receiving 5 subcutaneous injections of Id conjugated to KLH in SAF adjuvant, 4 had de novo intermediate-grade disease, and 4 had disease that transformed from indolent to more aggressive lymphomas. All had recovered their peripheral white blood cell counts prior to vaccination. Patient 7 received incomplete SAF (ISAF) as adjuvant for all 5 vaccinations. ISAF lacks the antigenic protein threonyl-muramyl dipeptide, but has been found to have comparable efficacy in stimulating immune responses [26].

Seven patients were enrolled into the dendritic-cell vaccination trial, but 3 developed progressive lymphoma within 6 months of the HDCT procedure and were therefore excluded from vaccination. Four patients received the dendritic-cell vaccination regimen. All had indolent histologies at diagnosis, and only Patient 9 had disease that transformed to a more aggressive histology at the point of tumor progression. The first dendritic-cell reinfusion was given approximately 6 months following ABMT. All 4 patients had peripheral white blood cell counts that recovered to normal levels by the time of vaccination. Patient 11 had failure of engraftment of his megakaryocytic lineage with persistent severe thrombocytopenia (20,000-30,000 platelets/mL) despite experimental treatment with thrombopoietin. This condition did not delay or significantly complicate his vaccination regimen beyond the need for prophylactic platelet transfusions prior to the leukapheresis procedures.

### Toxicities

All protein vaccinations were well tolerated. Patients noted moderate fever, myalgia, and fatigue for several days following the injections, with local erythema and tenderness lasting up to 1 week. No limiting, sustained, or delayed toxicities were identified, and no patients required any adjustment in formulation or schedule secondary to toxicity. All reactions to vaccination were consistent with prior experience, and were characteristic of the SAF adjuvant alone [6].

The dendritic-cell infusions were not associated with any infusional toxicities, consistent with prior experience [7]. The subcutaneous protein vaccine formulation for this protocol used ISAF (previously defined) as adjuvant, which was very well tolerated with mild local reactions of significantly milder severity compared to those with SAF. Each patient who started a vaccination regimen completed it without interruption, dose adjustment, or delay.

### Immune Responses

***Id-Adjuvant Vaccination***. The patients who received vaccination with Id coupled to KLH in adjuvant (Tables 1 and 2, Patients 1-8) all mounted robust immune responses (both humoral and proliferative) against KLH (Table 2), supporting the capacity of the immune system following HDCT to

**Table 2.** *Immune Responses and Freedom From Progression**

| Patient No. | Anti-KLH | | Anti-Id | | DFS, y† |
|---|---|---|---|---|---|
| | Humoral | Proliferative | Humoral | Proliferative | |
| 1 | + | + | – | + | 11.5+ |
| 2 | + | + | + | – | 8.0+ |
| 3 | + | + | + | – | 9.0+ |
| 4 | + | + | + | – | 1.3 |
| 5 | + | + | + | – | 1.0 |
| 6 | + | + | + | – | 6.5+ |
| 7 | + | + | + | – | 6.0+ |
| 8 | + | + | - | – | 5.8+ |
| 9 | + | + | + | – | 2.6 |
| 10 | + | + | + | – | 1.3 |
| 11 | + | + | + | + | 4.5+ |
| 12 | + | + | – | – | 1.0 |

*Id indicates idiotype; DFS, disease-free survival.

†DFS measured from myeloablative therapy to disease relapse. Ongoing DFS is denoted by a plus sign (+).

react against a strong antigen. Seven of these patients also mounted Id-specific humoral or cellular responses (Table 2).

Specific humoral responses against the idiotype could be measured in 6 patients of the Id-adjuvant vaccination group. Of the remaining patients, 1 developed a nonspecific response (detectable IgG binding to both autologous Id and class-matched control Ig), and 1 patient failed to develop any evidence of stimulated humoral immunity. One of the 8 Id-adjuvant vaccination patients developed significant specific cellular proliferative responses, and 1 developed a specific response that was on the borderline of significance. In total, 7 of 8 patients who received the Id-adjuvant vaccination developed either humoral or cellular Id-specific responses (Table 2).

***Dendritic-Cell Regimen.*** The second group of patients received the pulsed dendritic-cell and Id-KLH combination regimen (Tables 1 and 2, Patients 9-12). All 4 patients mounted both humoral and proliferative immune responses against KLH following the conjugated-protein vaccinations (Table 2). Three patients mounted specific humoral responses against their Id proteins. Patient 11 made a specific T-cell proliferative response. Patients 9 and 10 evidenced particularly robust but nonspecific cellular proliferative responses against the Id, with significant proliferation against control class-matched Ig. Patient 12 did not mount any measurable cellular response, although it is notable that this patient provided signs of an increasing lymphoma burden during the vaccination period and developed a clinical relapse shortly after vaccination. This suggests that his tumor was progressing subclinically even at the start of vaccination, which may have suppressed his ability to mount a tumor-specific response. In total, 3 of 4 patients developed either humoral or cellular Id-specific responses.

### Clinical Follow-up

The median follow-up following Id-adjuvant vaccination is >6 years after HDCT, ranging from 3 to >11 years. Only 2 of the 8 patients have relapsed, both early after completion of the vaccinations with rapidly progressive aggressive-histology disease. One patient who received the dendritic-cell regimen continues without relapse, now for more than 4 years after HDCT.

***Antigen Expression at Relapse.*** When possible, tumors were sampled at relapse and assessed for expression of the idiotypic antigen. None of the patients in the protein vaccination trial had tumor available for evaluation. Of the patients receiving the dendritic-cell vaccination, all 3 of the tumors that relapsed after vaccination expressed the idiotypic clone from their original indolent lymphoma, as defined by expression of the same Ig isotype and identity of the complementary DNA (cDNA) sequence of the CDR3 of tumor Ig heavy-chain cDNA.

## DISCUSSION

Current therapeutic options for both indolent and aggressive B-cell NHL are not curative for most patients and innovative treatments are needed. Idiotype vaccination shows promise in this disease, but experience suggests that the presence of clinically detectable disease may block or prevent the development of an immune response against the vaccine, as evidenced by the low frequency of immune responses identified in patients who had residual lymphoma at the time of vaccination [6]. Based on these observations, an effective approach will require either a more potent vaccine, or a more potent method to reduce the tumor burden. High-dose chemotherapy, although not in itself curative for the majority of patients, can provide maximal tumor reduction in most types of lymphoma, and may be a superior preparative regimen for therapeutic antitumor vaccines.

Models of marrow transplantation have shown that the murine immune system can reconstitute and mount efficacious immune responses as early as 2 weeks after myeloablative therapy [17,27]. These 2 studies represent experiments in a syngeneic murine marrow transplantation model and suggest that tumor-specific T-cell activation develops in the early posttransplantation period with possible beneficial effect on tumor-free survival. Immunization in the immune reconstitution period may augment this effect [28]. These data suggest that vaccines may be more effective at inducing antitumor immunity in the posttransplantation immune recovery period than in other clinical settings. Current evidence suggests that immune reconstitution in humans following myeloablative therapy recapitulates the establishment of immunity in the neonatal setting [29]. Part of this process involves the gradual recovery of a broad repertoire of B and T cells. The time frame for this reconstitution is driven by both innate and therapeutically administered cytokines. It is recognized that even in an autologous setting a form of graft-versus-host disease can develop, consistent with a hyperactivity of immune mechanisms, supporting the use of vaccination during the recovery phase after myeloablation [30].

Clinical experience with vaccination after HDCT with autologous marrow reconstitution is very limited. Attempts to use a dendritic-cell vaccination regimen with multiple myeloma have been successful in stimulating cellular Id-specific immune responses in a small percentage of patients, predominantly those in complete remission following HDCT [25,31]. Unfortunately, HDCT may have only a limited ability to induce complete regressions in patients with myeloma. In contrast, in B-cell NHL, it is frequently possible to achieve complete remission after myeloablative therapy, even in those patients with aggressive and multiply recurrent tumors.

The experience described herein clearly demonstrates that the immune system can reconstitute its ability to respond to both a strong xenoantigen (KLH) and a weak autoantigen (Id) following HDCT with autologous stem cell rescue. The majority of patients were able to mount humoral responses, similar to those that correlate with improved outcome in the nontransplantation setting [6]. Some patients were able to mount Id-specific cellular proliferative responses. The patients did not show any clinical signs of autoimmunity against Ig or other self antigens. These observations all serve to support the potential for vaccination in the posttransplantation setting.

All patients studied had aggressive disease and would have been expected to have a poor prognosis even in the context of having received HDCT. It is encouraging that 7 of these 12 patients have experienced prolonged remissions. Nevertheless, it is not possible from this limited experience to determine the contribution of the vaccine to this favorable outcome.

We cannot compare the 2 vaccine regimens within these protocols due to the small numbers and nonhomogeneous

patient population. The general experience and potency of dendritic-cell vaccinations supports their continued experimental development. With further improvement in vaccine technology, possibly including more efficacious adjuvant formulations, optimized dendritic-cell preparations, and the addition of cytokines, our ability to induce immunity against tumors will improve.

This experience suggests that vaccination in the post-myeloablative setting is safe and feasible in patients with NHL. In addition, patients in the posttransplantation setting have immune reconstitution sufficient to mount measurable antitumor responses. Myeloablative therapy permits the achievement of maximal tumor reduction and creates an opportunity during the immunologic recovery period to maximize the immune response against weak tumor-related antigens. As our understanding of this immune recovery increases, our ability to integrate immunologic manipulations will provide an opportunity to optimize active immunotherapy.

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